CHEMOTHERAPY IN BACILLARY DYSENTERY: EXPERIENCE IN THE EDINBURGH EPIDEMIC 1943-45.

A Thesis submitted for the Degree of
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INTRODUCTION.

The results of the use of drugs of the sulphonamide group in the treatment of bacillary dysentery have been extensively studied both in this country and in the United States; they have also been studied in the treatment of the disease in the forces in the Middle East and other theatres of war.

There are many factors which make it difficult to interpret the results of the use of any drug in the treatment of bacillary dysentery in Great Britain. First of all the disease, as seen in this country, is typically a very mild one, although cases of all grades of severity are encountered. Usually the illness lasts for only a few days, diarrhoea with loose stools containing blood and mucus being the main symptom; but there are many cases which are so mild that only a few loose stools are passed, and there is the odd very severe case endangering life itself. It will therefore be difficult to demonstrate the effect of drugs in the very mild cases, as they will almost have recovered before any drug could take effect, and the presence of a large number of such cases in any series will mask the effect of the drug on the more severe cases; also it will be necessary to draw definite conclusions only from strictly controlled series of cases in any given outbreak, as by that means alone can allowance be made for/

for the effect of varying severity of the disease in different epidemics. Further, it will be necessary to have a sufficiently large number of cases for study, so that there would be a chance of observing cases of all grades of severity. Then the different bacteriological types of dysentery bacilli respond differently to sulphonamide treatment so that, if the results of treatment are to be of real value, all cases studied must be examined bacteriologically.

The efficacy of the drugs in preventing the occurrence of, or reducing the number of convalescent carriers, and in rendering persistent carriers bacteriologically negative is of as much importance as, indeed is, in many cases, of more importance than, its effect on the clinical course of the disease. This can only be studied if adequate clearance tests are used, and if the cases are kept under observation for a sufficient length of time after treatment, so that the intermittent carrier will be detected, and also the case which relapses bacteriologically some time after treatment has been stopped. For this purpose it will also be necessary to see that chances of re-infection are reduced to a minimum and, once again, controls are really necessary as the convalescent carrier rate varies with different types of organism, in different epidemics and with the age-group to which the patients belong.

The/

The clinical features of the disease as seen in the United States, at least around New York, have been described recently by Hardy and Watt (1944) in a review of 1,500 cases. It would appear that the vast majority of the cases there are similar in severity to those in this country. They suggest the name "Shigellosis" for the disease as a great many of the cases never suffer from "dysentery" which, strictly speaking, means "blood and mucus in the stools". Nevertheless, many of the cases described in American literature are of a severity rarely seen in this country.

Manson-Bahr (1942) also points out that many cases of infection with dysentery bacilli never have blood and mucus in the stools even in countries where the disease is often very severe. The published work on the treatment with sulphonamides of bacillary dysentery in the forces contains many accounts of very severe cases, but also, in some the disease was very similar to that seen in this country. Scadding (1945), in particular, describes treatment in an outbreak of relatively mild cases in the forces, and emphasises the difficulties of assessing the results of treatment in such cases.

In Part I. of this thesis some of the literature recording the results of treatment of bacillary dysentery with sulphonamides is summarised and the conclusions which may be drawn from the published work are/

are discussed.

In Part II. the results of the treatment of 1000 cases with salts, sulphaguanidine or succinyl sulphathiazole at the City Hospital, Edinburgh, are recorded and discussed, together with the results of blood sulphaguanidine and succinyl sulphathiazole estimations carried out on some of the cases. All of these cases were examined and observed by me while I was Senior Assistant at the hospital.

The results obtained by myself together with those of others are discussed in Part III. and recommendations for the chemotherapy of the disease as seen in this country are made.

PART I.

WORK DONE IN BRITAIN.

In Great Britain Anderson and Cruickshank (1941) described the results of treatment of 41 cases of bacillary dysentery with sulphaguanidine, and compared them with 55 cases occurring in the same epidemic which had no specific treatment; from 59 of the cases studied the Flexner (z and x) dysentery bacillus was isolated; the dosage of the drug used was at first gm II t.i.d. for 4 days followed by gm III daily for 2 days but, as the drug was very well tolerated, the dose was increased to gm IV daily for up to a week if necessary. The clinical results were good when compared with the controls and, out of 16 treated cases examined bacteriologically after treatment, three were positive but two became negative after a further week of the drug; while, out of 17 control cases similarly examined, 8 were positive after the first week, 5 in the third week, 2 in the fourth and one in the sixth week. It will be seen that the dosage of drug used here is small compared with later series and the controls were not treated at exactly the same time as the other cases studied, but still the sulphaguanidine appears to have given superior clinical results, and to have reduced the number of convalescent carriers. The patients were all adults and the specimens for bacteriological/

bacteriological examination were taken from the rectum with a loop and grown on a desoxycholate-citrate medium; but all the cases were not confirmed bacteriologically. Clay (1943) compared the results of treatment with sulphaguanidine, sulphanilamide and salts in 273 cases of bacillary dysentery, 151 being Flexner infections and 122 Sonne infections; sulphaguanidine was given in doses of 0.5 gm. per kilo in the first 24 hrs followed by 0.1 gm. per kilo given in three doses for 4 days; sulphanilamide was given in doses of gm I 4 hrly for 4 days and then gm. I t.i.d. for 4 days; the salts treatment consisted of 3II of sodium sulphate twice a day; the standard of clearance used was 3 consecutive negative stools taken at twice weekly intervals. The stay in hospital and the number of days during which the stools remained positive were reduced by half in the sulphaguanidine - treated cases as compared with those receiving no chemotherapy, except in the case of Sonne convalescent carriers; in the sulphanilamide-treated cases both the stay in hospital and the length of time during which stools remained positive were increased. The effect of sulphaguanidine in reducing the convalescent carrier rate, especially in Flexner infections, was marked in this series of cases.
Swyer (1943) got good results both as regards clinical effect and bacteriological clearance with the use of sulphapyridine in 57 Sonne cases, when he compared them with/

with 35 controls; none of the sulphapyridine-treated cases relapsed bacteriologically while six bacteriological relapses occurred in the control series in from 7 to 36 days. Jamieson et alia (1944) studied the results of treating 200 cases of bacillary dysentery comprising Flexner (73) Newcastle (78), Sonne (39) and mixed infections (10). 100 cases got sulphaguanidine, 30 gms on the first day and then 8 gms. a day for 4 days; 50 cases were treated with a chalk mixture; and 50 cases with aperients, castor oil followed by milk of magnesia for children, who made up the bulk of the cases, and sodium sulphate for adults; the standard of clearance used was 3 consecutive negative stools at twice weekly intervals, the first specimen being taken 4-6 days after clinical cure. They considered that sulphaguanidine gave the best results so far as clinical cure was concerned, and the percentage of cases positive after treatment was reduced from 50% in the cases treated with salts and chalk to 30% in those receiving sulphaguanidine. Although the numbers of cases of the different bacteriological types of dysentery receiving each form of treatment are small in this series, the results taken as a whole are sufficiently striking. Another experiment carried out in this country where controls were used was that of Vollum and Wylie (1946) who treated an outbreak of Sonne dysentery in two boy's schools with succinyl-sulphathiazole,/

succinyl-sulphathiazole, in six daily doses of 1 gm. for 5 days. They first treated 10 cases which were not isolated and found that 8 out of the ten were bacteriologically positive again in 4 weeks. They then treated all of the 37 cases in one school and left the 33 cases in the other school untreated as controls; 36 out of the 37 treated cases were negative after treatment while 11 out of the 33 controls continued to excrete the organism. They considered that re-infection was the factor in the poor results in the first 10 cases, and that succinyl sulphathiozole is the best available drug for treating Sonne infections. Several other British workers have published the results of treating bacillary dysentery with various sulphonamide drugs without the use of controls. Masefield (1941) treated 16 moderately severe adult cases of Flexner dysentery with sulphapyridine, giving a total dosage of 13.5 gms. in 5 days. He found they were all bacteriologically negative by the 5th day using 4 consecutive negative rectal swabs as the standard of clearance; and he and his staff considered that the illness was shortened by 7 days when compared with previous outbreaks in the same mental hospital. While, of course, it is possible that this was a milder type of/

of dysentery, the results suggest that the sulphapyridine had a beneficial clinical effect, and also that it resulted in early bacteriological clearance. Smith (1944) records an interesting experiment with the dosage of sulphaguanidine in 10 Flexner cases and 34 carriers occurring in adult women. He gave a total dosage of 142 gms. in 10 days, 24 gms. being given daily for the first 3 days. The results of treatment were very satisfactory, all of the cases being bacteriologically negative at the end of the course as judged by the getting of 3 negative rectal swabs and 2 negative stool specimens over a period of 14 days after treatment; but 21 toxic rashes developed about the 9th day of treatment. He found that eight out of twelve of those patients reacted to a sensitisation dose of sulphaguanidine although there was no response to sensitisation doses of other sulphonamides. He suggests that the guanidine radical may be the sensitizing agent. It is interesting to note that, with this dosage of sulphaguanidine, blood levels of 8 mgms. per 100 c.c. were got at first, and that the blood level fell to under 2 mgms. per 100 c.c. as the dose of the drug was reduced. Swyer (1945) compared the results of treatment in Sonne dysentery with three sulphonamide drugs, sulphanilylbenzamide, sulphanilylamidobenzamide and succinyl sulphathiazole. He treated 179 cases in all, 41 with the first drug mentioned above, 112 with the second and 26 with the third; the

dosage/

dosage was the same for all drugs and was according to the weight of the patient an adult getting 20 gms. in the first 24 hrs. and then 6 gms. a day for 4 days; all the patients were observed in hospital for a period ranging from 4.5 days to 9 days before treatment was begun and, after treatment, they were observed for a period of 10.9 to 14.8 days; in the first series daily specimens of faeces and rectal swabs were examined and in the second and third series similar examinations were carried out on alternate days during all three periods. In the first series the stools were very markedly improved in 24-48 hrs., in the second series they were also markedly improved by that time, but no great improvement in stools was noted in the third series. Bacteriological clearance was obtained in the first series in an average of 1.8 days, in the second series in 3.6 days for those cases which got full dosage of the drug, and in 2.5 days for some of the cases which only got half dosage, while in the third series the time for bacteriological clearance was 2.4 days. Cases which relapsed bacteriologically, by which was meant cases giving a positive rectal swab after two consecutive negative ones, are not included in the above results. There were 3 such cases (7.3%) in the first series, 11 (13.4%) in the cases of the second series which got full doses and 1 (3.3%) in the cases of/

of the second series which got half doses, and 9 (34.6%) in the third series. Swyer points out that the efficacy of the drugs, particularly in clearing up carriers, was in direct proportion to the degree of absorption of drug from the intestine. The number of cases treated with succinyl sulphathiazole, however, is small compared with the other series, the dose, namely 44 gms in 5 days is also small for this drug and the high proportion of bacteriological relapses in this group may be due to the presence of the drug in the faeces affecting the isolation of the organism, as specimens were taken all through the course of treatment. This factor would not operate so markedly with the other drugs which were absorbed to a greater extent. Phthalyl-sulphathiazole, in doses of 15 gms. on the first day followed by 4 gms a day for 4 days, was used by Brodie et alia (1946) in the treatment of 48 bacteriologically proved cases of Sonne dysentery and 40 clinical cases; 60 of the cases were under 10 years of age; the Sonne cases were cured clinically in 8.73 days and 20.8% were positive in convalescence; the standard of clearance was 3 bi-weekly negative specimens got 4 days after the drug had been stopped. Caldwell and Hardwick (1943) published the case of a woman of 36 who was a persistent carrier of Flexner dysentery for 18 mths., in spite of four courses of sulphaguanidine, the/

the first consisting of 9 gms a day for a month, and the others of 60 gms in 7 days; after that 9 gms of succinyl sulphathiazole were given for 7 days after which no further positive specimens were got. Although no definite conclusions can be drawn from one case which may have simply cleared up spontaneously after 18 mths, it does look as if succinyl sulphathiazole was beneficial here where sulphaguanidine had failed.

CONCLUSIONS FROM THE BRITISH WORK.

It will be seen that all those British workers who treated bacillary dysentery with sulphonamide drugs, and who treated a control series of cases with salts or a chalk mixture for comparison, were of the opinion that the sulphonamides gave results superior to the other methods both as regards clinical effect and bacteriological clearance. Sulphaguanidine gave better results in Flexner than in Sonne infections especially so far as bacteriological clearance was concerned; but sulphapyridine and succinyl sulphathiazole gave good results in Sonne infections. The series of cases treated without controls showed that sulphapyridine gave good results in Flexner infections, that phthalyl sulphathiazole probably gave better results in Sonne infections so far as bacteriological clearance was concerned than sulphaguanidine, and that/

that sulphanilylbenzamide and sulphanilylamidobenzamide also gave good results in Sonne infections. But in all those series, there were cases which were not bacteriologically negative after several courses of the drugs, and in no case did any particular drug render all cases bacteriologically negative if a sufficiently large number of cases was studied.

WORK DONE IN AMERICA.

During the same period, that is from 1941 onwards, the treatment of bacillary dysentery with the sulphonamides was being studied in the United States, and American literature provides several accounts of the results of that work. Lyon (1941) found that he got clinical improvement compared with controls when he treated 23 "severe or very severe" cases with sulphaguanidine and used 23 similar cases as controls; half of the cases were proved bacteriologically but he did not study the bacteriological effects of treatment. Hardy et alia (1942) got good results when they treated 57 Flexner and Newcastle cases and carriers with sulphaguanidine, but they had one carrier who still excreted the organism after 330 gms of the drug in 22 days. Hall (1942) considered that good clinical results were got in a small series of 30 cases of Hiss infection in Kentucky. Most of the cases were children and the drug used was sulphaguanidine, half of the cases,which were used as controls, receiving no specific treatment. Opper and Hale (1942) treated 15 Flexner cases and 18 carriers with sulphaguanidine in the small dose of 4 gms daily for a week; all cases were bacteriologically negative at the end of the course, 4 relapsed but were cleared by a further course. They compare those results with 18 cases and 20 carriers treated/

treated in 1939–40 without sulphaguanidine when 57% of the cases excreted the organism for over a month. This is, of course, not a strictly controlled series of cases, and the dose of the drug is very small. Smyth, Finkelstein et alia (1943) concluded that both sulphaguanidine and succinyl sulphathiazole had some value in treating symptoms, from the treatment of 30 cases of Flexner dysentery, 10 with sulphaguanidine, 14 with succinyl sulphathiazole and 6 without specific treatment as controls. There were six deaths in the series, 4 in the controls, 1 treated with sulphaguanidine and 1 treated with succinyl sulphathiazole. So far as the use of sulphathiazole is concerned Rubens, Kaplan et alia (1943) thought that it was of definite value in the treatment of clinical dysentery in children, it reduced the number of days of diarrhoea from 8.8 to 2.9; but Yannet and Leibovitz (1942) got poor results from its use in treating 44 Sonne cases and 13 carriers; 27 patients got sulphathiazole and the rest were used as controls, and the time taken for bacteriological clearance was longer in the drug-treated cases than in the controls. Roberts and Daniels (1943) found that succinyl sulphathiazole reduced the carrier rate from 18.2% to 2.6% in 225 cases of Boyd 88 infection, although it did not ameliorate or shorten the illness which was of about 4 days duration. The dose used

was/

was 0.25 gm per kilo as a first dose and then 0.25 gm. per kilo daily in six doses till the temperature had been normal for 2 days and diarrhoea had stopped for 2 days and 89 cases got the drug while 136 were used as controls. Phthalyl sulphathiazole was used in the treatment of 26 cases out of 59 Flexner, Schmitz and Sonne infections by Sandweiss (1944). He gave a dose of 0.1 gm. per kilo daily in 5 doses for an average of 14 days and found that it had no effect on the carrier state, as 30% of the treated cases were still positive after treatment, and 56% of the treated cases observed for a longer period were positive for 8-40 wks. compared with 33% of the controls. This is not as good a result, so far as bacteriological clearance is concerned, as that got by Brodie et alia (1946) who found only 20.8% of 48 Sonne cases bacteriologically positive after 31 gms. of the drug in 5 days but the number of cases is small in both series. Painton and Hantman (1945) treated 181 Sonne cases, 28 with sulphaguanidine, 71 with succinyl sulphathiazole, 49 with phage and 33 without any specific treatment. Succinyl sulphathiazole gave the best results with 1.5% of failures so far as bacteriological clearance was concerned; sulphaguanidine in doses of 8 gms. a day for 7 days gave one failure in 7 and in smaller doses of 4 gms. a day for 7 days it gave the same results as the phage-treated and untreated cases, namely 18-24% of failures. The dose

of/

of succinyl sulphathiazole used was 0.25 gm. per kilo for 7 days. The number of cases treated with sulphaguanidine was small and, even the bigger dosage used, was small but nevertheless, compared with the other methods of treatment, the results with succinyl sulphathiazole were by far the best. Several other American workers have published uncontrolled series of cases. Hardy, Burns and Decapito (1943) reviewed the treatment of 501 cases and carriers of Flexner, Sonne and Schmitz organisms with sulphaguanidine, succinyl sulphathiazole, sulphadiazine and sulphathiazole, and they concluded that all four drugs controlled the symptoms and modified the disease; they considered that sulphadiazene gave the best results and then succinyl sulphathiazole especially in Sonne carriers. Also Hardy and Watt (1944) in their review of 1,500 cases made up of Flexner, Sonne and other organisms, when ten different sulphonanides were used, considered that the poorly absorbed sulphonanides were no more successful than the others except that succinyl sulphathiazole was better for Sonne infections which were the most difficult to treat. Eisenhoff and Goldstein (1943) treated 33 Sonne cases and 50 carriers with 4 different sulphonanides, sulphathiazole, sulphadiazine, sulphaguanidine and succinyl sulphathiazole: 8 cases were positive after the course, 3 each after sulphathiazole and sulphaguanidine and 2 after succinyl sulphathiazole: 2 of these/

those failed to clear with a further course of sulphadiazine, so once again it is seen that none of those drugs will clear all cases. Marshall et alia (1941) published good results in an uncontrolled series of dysentery cases treated with sulphaguanidine, and Barker (1943) studied the treatment of 5 dysentery carriers, 2 were Flexner infections and 3 alkalescens and they were treated with succinyl sulphathiazole. He concluded that a dosage of 0.1 gm. per kilo was inadequate but that 0.25 gm. per kilo was effective. Scott (1943) controlled an outbreak of Sonne dysentery in a home for mentally defective children with as little as 0.5 gm. t.i.d. of sulphaguanidine.

CONCLUSIONS FROM THE AMERICAN WORK.

American workers, therefore, have come to much the same conclusions as the British, and some of them were treating a more severe type of case. They found that sulphonamides gave results superior to the older methods of treatment, that Flexner infections were easier to treat, especially to clear bacteriologically, than Sonne infections; that sulphathiazole and sulphadiazine probably gave as good results as sulphaguanidine and succinyl sulphathiazole, except in Sonne carriers where succinyl sulphathiazole proved more effective; and that some carriers were very resistant to any sulphonamide drug. There were two small series of cases /

cases, where controls were used, where no benefit was seen from the use of the drug; one where sulphathiazole was used to treat Sonne infections and one where phthalyl-sulphathiazole was used in Flexner, Sonne and Schmitz infections. Also no beneficial clinical effect was noted in a series of Boyd 88 infections when succinyl sulphathiazole was used and a comparison was made with untreated controls, but the convalescent carrier rate was much reduced.

WORK DONE IN THE FORCES.

Much of the bacillary dysentery which occurred in the forces and which was treated with sulphonamides was of the more severe Shiga type, but the results of treatment of some milder cases have also been published. Paulley (1942) studied the clinical results of the treatment of 173 cases, mostly Flexner infections, but some Sonne and Schmitz as well. He states that it had been concluded from a study of the treatment of dysentery in the Middle East that "do nothing and fluids was as good treatment at least as salines." He treated 60 cases with salines, the average period of stay in hospital being 14.6 days; 25 cases got sulphaguanidine, the stay in hospital being 5.36 days; 43 cases, and later another 30 got sulphapyridine, the stay in hospital being 4.26 and 4.96 days respectively; and 15 cases got kaolin, the stay in hospital being 6.1 days. He concluded that sulphonamides gave results superior to the other methods and that sulphapyridine was better than sulphaguanidine. Scadding (1944) got equally good results in the treatment of 358 mild cases with sulphanilanide, sulphapyridine and sulphaguanidine; the clinical results only were studied and the infections were Shiga, Sonne, Flexner and some unidentified organisms but all were mild cases. Later Scadding (1945) treated 390 cases, 99 of whom were proved bacteriologically/

whom were Shiga infections, with sulphaguanidine. They found marked clinical improvement especially in severe cases and rapid healing of the intestine with reduction in toxaemia and a feeling of well-being. Only severe cases were treated and the best results were got in acute cases. Rutler and Marberg (1941) got good clinical results with sulphapyridine in the treatment of 20 severe or moderately severe cases, mostly Flexner infections, in Haifa. They state that the stools were bacteriologically negative when found but do not give the standards of clearance employed. Bulmer and Priest (1942) claimed good results in an uncontrolled series of 77 cases treated with sulphaguanidine. Brewer (1943) treated 77 severe cases, 26 were acute of whom six were Flexner infections, and 51 were chronic of whom fourteen were Flexner infections: they were given sulphaguanidine 7 gm. and then 3.5 gms. 4 hourly till two days after the stools were normal, and the chronic cases got 17.5 gms. daily for 8 days, a dosage which he considered essential for such cases. The clinical results were good but treatment must be given until the bowel is healed; and the writer considered sigmoidoscopy essential in the chronic cases. No controls were used here but the results seem to have been striking in severe cases. Brewer (1944) also got good results with the use of succinyl sulphathiazole, 44 gms. in 5 days, in the treatment of 16 Sonne cases which were still/

still bacteriologically positive 1-3 wks. after treatment: 9 of them had had sulphaguanidine for 5 days. 15 of the cases were negative in 5 days and the other case was negative after a further course of the drug. 3-8 specimens or rectal swabs were examined 6-20 days after treatment. The drug may, of course, have cut short the carrier state but, on the other hand, a big proportion of Sonne cases would be negative in that time without specific treatment. Osborn and Jones(1944) published the results of treating an outbreak of Sonne dysentery in a hotel being used as a Naval Officer's treatment establishment. They got better clinical results when they increased the dose from 18 mgm. in 48 hrs. followed by 5 gms. daily to 30 gms. in 48 hrs. followed by 7.5 gms. daily but 8 out of 71 cases treated did not become negative. Ferriman and Mackenzie (1944), who used sulphaguanidine, sulphathiazole and sulphanilamide in the treatment of 56 cases of dysentery, 27 being proved bacteriologically, thought that sulphathiazole was more effective than sulphaguanidine and should therefore be used in severe cases, while sulphaguanidine, being less toxic, should be used in mild cases; sulphanilamide gave almost as good results as sulphaguanidine. Fairbrother (1944) found that 10% of those with a recent history of diarrhoea were carriers of dysentery bacilli, when he examined stool specimens/

specimens from 2,500 Italian prisoners of war; and many carriers were probably missed as only one specimen was examined in many instances. The majority of those were Flexner infections and most of them cleared with one or at most two courses of sulphaguanidine. He found that 52% of cases of mild Sonne dysentery cleared bacteriologically in 2 weeks without sulphonamide treatment and, by 3 weeks, 60% of cases had cleared. The treatment of the remaining carriers with sulphaguanidine (22 cases) and succinyl sulphathiazole (17 cases) was not entirely satisfactory. The dosage of sulphaguanidine was 81-90 gms. in 8 or 9 days and of succinyl sulphathiazole was 81-90 gms. in 8 or 9 days, and the standard of clearance used was very high, namely 12 successive daily negative specimens taken some days after sulphonamide treatment had been stopped.

CONCLUSIONS FROM THE WORK DONE IN THE FORCES.

The most striking feature which is noticeable from reading the records of the use of sulphonamides in the treatment of bacillary dysentery in the forces, is the practically unanimous opinion that almost any of the sulphonamides modify the clinical course of the disease. Those who have used them in severe cases are most convinced of their value. The bacteriological results of treatment were not often studied but Fairbrother's results indicate that the carrier state is very common.

GENERAL CONCLUSIONS FROM THE LITERATURE REVIEWED ABOVE.

1. Clinical effect of sulphonamides on bacillary dysentery.

From a study of the published work on the subject there would seem to be no doubt about the fact that drugs of the sulphonamide group have some beneficial effect on the clinical course of the disease. This conclusion has been arrived at by both British and American workers, although it is extremely difficult to demonstrate it in the mild type of case prevalent in this country and in parts of the United States; and it is the opinion held by those who have treated the much more severe type of the disease which occurs abroad. Although Scadding (1945) failed to demonstrate any significant difference on the course of the disease when he compared cases treated with sulphaguanidine with controls treated with a chalk mixture, he points out that the cases were very mild, and that he thinks that severe and chronic cases benefited from sulphadiazine. The only other workers quoted above who failed to demonstrate some beneficial clinical effect from the use of the sulphonamides were Roberts and Daniels (1943) who treated Boyd 88 infections with succinyl sulphathiazole, and Sandweiss (1944) who treated Flexner, Sonne and Schmitz infections with phthalyl sulphathiazole. They were working with small series/

series of cases and it may be noted they were using poorly absorbed sulphonamides. They used control series of cases.

Although much of the work in all parts of the world was done without the use of controls, many of the workers had an extensive experience of the behaviour of the disease before the introduction of sulphonamides which lends some weight to their clinical impressions.

2. Effect on convalescent carriers and discussion of standards of clearance.

The effect of the drugs in reducing the number of cases which become convalescent carriers and in shortening the time during which they continue to carry the organism can only be judged by the study of strictly controlled series of cases; and there also arises the question of what can be considered adequate standards of bacteriological clearance. Fairbrother (1944), from a study of Sonne carriers, considers that nothing short of 12 consecutive daily negative specimens or alternatively 12 successive negatives over a period of at least 3 wks. would be adequate. He also emphasises that the specimens must not be examined for at least 6 days after sulphonamide treatment has been stopped. This would mean that cases would be under observation for 3 wks. after treatment, an ideal which would not be easy/

easy to attain in hospitals but which might well be used for a study of the different sulphonamides in, for example, outbreaks of the disease in asylums or other institutions. It also presupposes the availability of the services of a first-class laboratory.

Many workers, however, have used quite reasonable standards of clearance, for example 3 consecutive negative bi-weekly specimens examined with the use of the modern highly selective media, and have demonstrated a definite reduction in the convalescent carrier rate in Flexner and Newcastle infections, for example: Anderson and Cruikshank (1941) using sulphaguanidine; Clay (1943) using sulphaguanidine; Jamieson and others (1944) using sulphaguanidine, and Hardy and others(1942) using sulphaguanidine. All those workers had control series of cases treated without sulphonamides.

Some reduction in the number of convalescent carriers has also been got in Sonne infections by Swyer (1943) using sulphapyridine; Vollum and Wylie (1946) using succinyl sulphathiazole; Painton and Hantman (1945) using succinyl sulphathiazole; but others have failed to demonstrate any such reduction in Sonne infections. Fairbrother (1944) using both sulphaquanidine and succinyl sulphathiazole in Sonne cases, and Yannet and Leibovitz using sulphathiazole in Sonne cases both failed to get any reduction in the convalescent carrier rate from the use of the drugs.

Several/

Several of the workers mentioned above have encountered resistant cases of both Flexner and Sonne infections which did not respond to repeated courses of sulphonamides.

3. Effect on persistent carriers.

There have been few adequate studies of persistent carriers, and it is here that it would be most difficult to demonstrate any effect, unless, of course, a drug were found which was effective in every case: no such drug has yet been found in any of the sulphonamides.

There would, therefore, seem to be some evidence for the statement that, when used in the treatment of acute cases of bacillary dysentery, the sulphonamides have been shown to reduce the number of cases which become convalescent carriers; but the effect is not so noticeable if treatment is delayed, and the treatment of persistent carriers, especially Sonne carriers, is unsatisfactory.

4. Relative merits of the different sulphonamides.

Concerning the relative merits of the different sulphonamides, good results have been got, both as regards clinical effect and bacteriological clearance, by the use of both the readily absorbed drugs and the less readily absorbed ones. In this country sulphaguanidine has been the drug most used by those who have published their results, and it has proved satisfactory/

satisfactory in Flexner infections; but Swyer (1943) got good results in a small series of Sonne infections with sulphapyridine, and Masefield (1941) likewise got good results in Flexner infections with sulphapyridine. Vollum and Wylie (1946) found succinyl sulphathiazole effective in Sonne cases and Brodie and others (1946) got better results, so far as bacteriological clearance is concerned, with phthalyl sulphathiazole in Sonne infections when they compared them with previous results with sulphaquanidine. American workers have got good results with sulphadiazine but found succinyl sulphathiazole most effective in treating Sonne carriers. Some of the workers treating the disease in the forces have likewise got good results with absorbable sulphonamides, for example Paulley (1942) with sulphapyridine, and Scadding (1944) with sulphapyridine and sulphanilamide; as well as with sulphaquanidine.

PART II.

PERSONAL EXPERIENCE OF THE TREATMENT OF BACILLARY DYSENTERY WITH SULPHAGUANIDINE AND SUCCINYL SULPHATHIAZOLE.

I. Between November 1943 and the end of 1945 there were admitted to the City Hospital, Edinburgh just over a thousand cases and carriers of bacillary dysentery from whom the dysentery bacillus was isolated; they constituted about half of the cases notified as suffering from dysentery. 479 of these were Flexner infections, 87 were Newcastle and 506 Sonne infections.

In 1943 and the first half of 1944 Flexner's bacillus was the predominant organism. Accordingly, it was decided to treat a series of Flexner infections with sulphaguanidine and, at the same time, to treat a control series with sodium sulphate.

Method of procedure.

Alternate admissions between Nov. 1943 and May 1944 were given sulphaguanidine and sodium sulphate, and only those cases from whom the infecting organism was isolated are included in the series. Altogether 143 cases were treated with sulphaguanidine and 142 with sodium sulphate.

Clinical/

Clinical features of the cases.

The cases were mostly very mild, usually having from a few days to a week of diarrhoea with blood and mucus in the stools, and accompanied by abdominal pain and general malaise. While a small percentage of the cases had a pyrexia of 102°F. or over on admission, the majority had very little pyrexia and, in almost all of them, the temperature was normal after 24 hrs. in bed. A few of the admissions were more or less symptomless carriers detected on routine rectal swabbing of contacts, but most of those had a history of recent diarrhoea. There were two deaths in this group of cases; one, a man of 33 yrs. with Parkinson's disease and poor general physique, died 7 days after admission from hypostatic pneumonia; the other, a man of 87 yrs., died 12 days after admission from myocardial degeneration. The first case had been treated with sulphaguanidine and the second with sodium sulphate, and both had recovered clinically from the attack of dysentery. They are not included in the series of cases as they were not bacteriologically negative at the time of death.

The dosage of sodium sulphate given was as follows:

TABLE I./

TABLE I.

	Under 2 yrs.	2-3 yrs.	4-10 yrs.	11-15 yrs	Over 15 yrs.
48 hrs.	10 grs. 4 hrly.	20 grs. 4 hrly.	30 grs. 4 hrly.	40 grs. 4 hrly.	60 grs. 4 hrly.
48 hrs.	10 grs. t.i.d.	20 grs t.i.d.	30 grs. t.i.d.	40 grs. t.i.d.	60 grs. t.i.d.
3 days	5 grs. t.i.d.	10 grs. t.i.d.	15 grs. t.i.d.	20 grs. t.i.d.	30 grs. t.i.d.
(6 days if blood and mucus still present)					

The dosage of sulphaguanidine was as follows:-

TABLE II.

	0-3 yrs	4-10 yrs.	11-15 yrs	Over 15 yrs.
Initial dose	1 gm.	1.5 gms.	2 gms.	3 gms.
then	1 gm. 4 hrly for 24 hrs. then 0.5 gm. 4 hrly.	1 gm. 4 hrly.	1.5 gms. 4 hrly.	2 gms. 4 hrly.
Total dosage	24 gms.	42.5 gms.	63.5 gms.	85 gms.

This course lasted for 7 days.

Aperients, other than sodium sulphate, were given if necessary during this course as sulphaguanidine was found to have a constipating action. The 2 a.m. dose was omitted and half of it was added to the 10 p.m. and half/

half to the 6 a.m. doses. The tablets were given crushed up and followed by a drink of milk or water.

General management.

The patients were put on to the above treatment on admission to hospital. They were given milk only while diarrhoea was severe, and then a light diet which was quickly increased to full diet as the condition improved. Abundant fluids were given by mouth, but none of those patients was sufficiently dehydrated to require the parenteral administration of fluid. Very little symptomatic treatment was required.

Stool specimens or rectal swabs were taken and sent for examination on three successive mornings after admission, unless a positive specimen from the patient had been examined at the University Laboratory before admission to hospital. Stool specimens or rectal swabs were again taken on two, or, for patients returning to other hospitals or institutions, on three successive mornings beginning on the morning after the last day of treatment. Two successive negative specimens or, for those returning to hospitals or institutions, three successive negative specimens were required for discharge from hospital; and, of course, the patient had to be free of all symptoms.

All the specimens were examined at the University of Edinburgh Bacteriological Laboratory where a desoxycholate-citrate/

desoxycholate-citrate medium was used. The vast majority of the cases were examined by the use of the rectal swab but, in some of the earlier cases, stool specimens were examined.

In all of the cases here studied re-infection as a factor in some of the cases which continued to excrete the organism for long periods cannot be eliminated, as the cases were not isolated separately.

Likewise 7 of the cases in the above series were re-admitted at a later date, either suffering from a clinical relapse or having been found to be bacteriologically positive, but re-infection outside hospital could not be eliminated. Five of those cases had been treated with sulphaguanidine and two with sodium sulphate.

Clinical results of treatment.

The mild nature of the majority of the cases makes it difficult to measure the effect of the two methods of treatment on the clinical course of the disease. The number of days during which the patients were kept in hospital has been used by some for comparison of results, but this number was frequently determined by factors not related at all to clinical recovery. So many of the cases had only slight pyrexia, or none at all, that the effect of the drugs on pyrexia likewise could not be used. Adequate records of the presence/

presence of blood and mucus in the stools were not kept owing to the difficulties of inspecting every specimen satisfactorily. The effect of the sulphaguanidine in producing a sense of well-being is difficult to measure, but was noticeable in the more severely ill cases and has been noted by many workers especially those treating very severe cases. The average number of days during which diarrhoea was present is a figure which can be used as a measure of the effects of the two methods of treatment. Diarrhoea was judged to have stopped when the stools were formed and not more than two were passed in the 24 hrs. In the cases treated with sodium sulphate the average number of days during which diarrhoea was present was 3.4, while in the cases treated with sulphaguanidine the number was 1.7.

This finding is similar to that of Clay (1943) who found that the number of days in hospital was halved in Flexner cases treated with sulphaguanidine compared with those treated with aperients. Also Jamieson and others (1944) found the average duration of symptoms 6.4 days in cases treated with aperients and 4.8 days in sulphaguanidine-treated cases. On the other hand they found that cases treated with a chalk mixture had an average duration of symptoms of only 4 days, but the number of Flexner cases treated with the chalk mixture was very small (6). Scadding (1945) had 17

Flexner/

Flexner cases and 17 Flexner controls in the series of cases he treated with sulphaguanidine, the controls getting a chalk suspension, and he found no difference in the course of the disease with the two methods of treatment. Paulley (1942) found that the stay in hospital was 14.6 days in 60 cases treated with salines, 5.36 days in 25 cases treated with sulphaguanidine and 6.1 days in 15 cases treated with kaolin. While, therefore, part of the effect of sulphaguanidine in reducing the average number of days of diarrhoea in the above series of cases may have been due to its constipating action, when the results are considered along with the findings of other workers, it would seem that sulphaguanidine reduces the length of time during which diarrhoea is present because of its effect on the cause of the intestinal infection.

Bacteriological results of treatment.

The bacteriological findings following treatment are shown in the following tables.

TABLE III./

TABLE III.

Type of Treatment	Sodium Sulphate.						Sulphaguanidine.					
Age Groups.	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.	All ages.	0.2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.	All ages.
No. of cases.	19	33	31	29	30	142.	17	27	23	39	37	143
Average No. of days positive.	16.4	15.4	12.8	11.5	18.2	14.7	6.3	8.6	10.9	5	10	8.1

The number of cases still positive after treatment in the series treated with sodium sulphate was 72, while in the series treated with sulphaguanidine it was 25.

They belonged to the following age-groups.

Discussion of those results.

It is realised that the standard of clearance used in this series of cases is inadequate for two reasons: first of all two, or even three, negative cultures, even on a highly selective medium, taken on successive days immediately after treatment would not eliminate the possibility of an intermittent excretor of the organism, nor of the patient becoming positive again about a week after treatment; the second point for criticism is that the two or three specimens or rectal swabs were taken immediately after treatment had been stopped, without allowing time for the elimination of sulphaguanidine from the bowel. The actual number of cases still positive after treatment was, therefore, probably higher than is shown, but some intermittent excretors would be missed in both series of cases, and the very big difference in the percentage of cases positive after the two different forms of treatment can hardly be accounted for by the presence of sulphaguanidine in the stools and nothing else. Furthermore, many of the third specimens taken on admission to hospital for diagnostic purposes, that is after 48 hrs. and often after 96 hrs. of sulphonamide treatment, gave positive results. It therefore seems that, in many cases, positive cultures can be got in the presence of considerable amounts of sulphonamide in the faeces.

It/

It will be seen from the above tables that the average number of days during which a positive culture was obtained in sulphaguanidine-treated cases was 8.1 compared with 14.7 days for the cases treated with sodium sulphate. Also 17.6% of the sulphaguanidine-treated cases were positive after the course compared with 50.7% of the sodium sulphate-treated cases. At the end of 56 days 1 of the sulphaguanidine-treated cases was still positive compared with 3 which had been treated with sodium sulphate.

Those results are similar to those of Clay (1943) who found that sulphaguanidine-treated Flexner cases were positive for an average of 6.6 days compared with 13.3 days positive for cases treated with aperients. They may also be compared with the findings of Jamieson (1943) who found that 30% of Flexner cases treated with sulphaguanidine were positive in convalescence compared with 50% of cases treated with sodium sulphate. He took the first specimen 4-6 days after clinical recovery and got three successive negatives at twice-weekly intervals. He was therefore taking specimens for a longer time after treatment which might account for the higher percentage of positives after sulphaguanidine.

II./

II. As the clinical results of treating Flexner dysentery with sulphaguanidine were better when compared with salts treatment, and, as the bacteriological results were definitely better, at least with the standards of clearance used, it was decided to treat all cases of Flexner dysentery admitted after July 1944 with sulphaguanidine. It was also decided to see whether the giving of a further course of the drug in cases still positive after the course would result in a shortening of the carrier period. Accordingly, from July 1944 to the end of 1945, 194 cases of Flexner dysentery were treated with the same course of sulphaguanidine and this was repeated once and more often if necessary until negative specimens were got. The second course was begun as soon as the positive report was received which was usually about four days after the specimen had been sent. The cases were again mild and the procedure as regards the taking of specimens was the same as before. One of the cases, a girl aged 6 yrs. was so ill and dehydrated on admission that she required an intravenous drip of glucose saline for 24 hrs. She was also given 2 gms. of sulphadiazine in the drip before treatment with sulphaguanidine was begun.

There was one death in this group of cases. It was in the case of a poorly nourished baby of $\frac{8}{12}$ yrs. who/

who died 8 days after admission to hospital, and again it is not included in the results shown below as clearance tests had not been taken.

The results of treatment are shown in the following tables.-

TABLE V.

Age Group.	0–2 yrs.	2–5 yrs.	5–12 yrs.	12–60 yrs.	Over 60 yrs.	All Ages.
No. of cases	66	31	24	40	33	194.
Average No. of days positive.	10.1	8.9	7.5	6.9	5.9	8.7

The number of cases still positive after one course of treatment was 27, that is 13.9%.

They belonged to the following age-groups.

TABLE VI.

Age Group.	0–2 yrs.	2–5 yrs.	5–12 yrs.	12–60 yrs.	Over 60 yrs.
No. of cases.	14	6	1	3	3
Percentage of total No. in group.	21.2	19.4	4.2	7.5	9.9

Two of those cases had three courses, their ages being 1 $\frac{3}{12}$, and 17 yrs, and one case had four courses the age in that case being $\frac{10}{12}$yrs. This case remained positive for 49 days.

Discussion of those results.

It will be seen that the average number of days during which the Flexner cases in this series remained positive was just about the same as before, 8.7 days compared with 8.1; while the percentage of cases still positive after the course was smaller, 13.9% compared with 17.6%.

The giving of further courses of sulphaguanidine did not result in all cases becoming negative at once, as two cases required three courses of the drug and one four courses before negative specimens were got. Those findings seem to support the view held by many that the results of treatment in the acute stage of the disease are better bacteriologically as well as clinically than the results of treating later cases or convalescent carriers. This view has been expressed by Anderson and Cruikshank (1941); Jamieson and others (1944); Fairley and Boyd (1942 and 1943); Brewer (1943) and Hall (1942) as well as by others.

The giving of further courses of sulphaguanidine, as was done here, is really a study of the treatment of convalescent carriers similar to that of Fairbrother (1944) and Brewer (1944) in the case of Sonne infections. In the series of cases here studied, however, the question of the development of drug resistance must be considered, as the cases were treated in the first instance/

instance with sulphaguanidine. Although an acquired drug resistance has been described in the case of dysentery bacilli, M.R.C. War Memorandum No.10 (1945), Fairbrother and Bumer (1944) could find no evidence of it in a study of resistant Sonne cases. It would seem as if, after the acute stage of the disease has passed, and especially if the carrier state is prolonged, the organisms become in some way less accessible to the drugs.

In the first series of cases described, numbering 143, where no further course of sulphaguanidine was given, 25 cases were positive after the course of treatment, 7 after 28 days and 1 after 56 days; in the second series, numbering 194, where further courses of sulphaguanidine were given, 27 cases were positive after the first course, 6 after 28 days and 1 for 49 days. There does not seem to have been any striking effect from the repeated courses of the drug, but the numbers are too small to justify any definite conclusion.

The one case which was given an initial dose of sulphadiazine intravenously improved clinically very rapidly, but, of course, the parenteral administration of fluid to such cases often brings about rapid clinical improvement. This rapid clinical improvement following the use of the readily absorbed sulphonamides sulphadiazine/

sulphadiazine and sulphathiazole had been previously noted at the City Hospital in acute cases before the present investigation was begun, but only a few cases were so treated.

III. Also in 1945, a series of 87 cases of Newcastle infection were similarly treated with repeated courses of sulphaguanidine if necessary. These cases were, on the whole, milder than the Flexner infections.

The results of treatment are shown in the following tables.

TABLE VII.

Age Groups	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.	All Ages.
No. of cases	40	21	17	9	0	87
Average No. of days positive.	7.2	6.3	5.6	5.1	0	6.8

The number of cases still positive after one course of treatment was 8, that is 9.2%. They belonged to the following age-groups.

TABLE VIII./

TABLE VIII.

Age Groups	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.
No. of cases	4	3	1	0	0
Percentage of total in group.	10	14.3	5.9	0	0

Discussion.

The bacteriological results of treatment in the Newcastle infections were better than in the Flexner cases but the cases were milder, and it must be noted that 9.2% of the cases were still positive after one course of treatment.

IV. In 1944 Sonne dysentery began to appear among the admissions to the City Hospital as well as Flexner and, by 1945, it became very much more prevalent than the Flexner type.

In 1944 a series of 180 cases of Sonne dysentery was treated with sulphaguanidine, the procedure being exactly the same as for the Flexner infections treated with repeated courses of the drug.

As succinyl sulphathiazole became available it was decided to treat a series of cases of Sonne infection using this drug, but it was only used in those cases which, on admission, were known to be Sonne infections. In 1944 and 1945, 142 Sonne cases were therefore/

therefore treated with succinyl sulphathiazole, in repeated courses where necessary, and in the same doses as sulphaguanidine. Another 184 Sonne cases admitted to hospital in 1945, but not diagnosed as Sonne infections before admission, were treated with a course of sulphaguanidine in the first instance but, if further courses were required, succinyl sulphathiazole was used.

Clinically the cases were of a type very similar to the Flexner cases previously described. There was one death in a child of $\frac{4}{12}$ yrs. in the series treated with sulphaguanidine; one death in a thin poorly-nourished child of $\frac{6}{12}$ yrs. in the series treated with sulphaguanidine and succinyl sulphathiazole, and 3 deaths in the series treated with succinyl sulphathiazole only. Two out of those three deaths were in children aged $\frac{3}{12}$ mths., one of whom died of pneumonia and the other patient was aged 76 yrs. and died of heart failure. The parenteral administration of fluid was required in three cases.

The bacteriological results of treatment in the three series of cases are shown below.

TABLE IX./

TABLE IX.

Age Group	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.	All ages.
No. of cases	64	53	20	29	14	180
Average No. of days positive.	10.35	9.1	6.6	6.8	8.1	8.8

The number of cases still positive after one course of treatment was 38, that is 21.1%.

They belonged to the following age-groups.

TABLE X.

Age Group	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.
No. of cases	19	9	3	4	3
Percentage of total No. in group.	29.7	17	15	13.8	21.4

TABLE XI.

Age Group.	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.	All ages.
No. of cases.	63	48	18	38	17	184
Average No. of days positive.	13.2	9.9	9.8	6.4	4.9	9.4

The number of cases still positive after one course of treatment was 56, that is 30.4%.

They belonged to the following age-groups.

TABLE XII./

TABLE XII.

Age Group	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.
No. of cases.	32	13	7	3	1
Percentage of total No. in group.	50.8	27.1	38.8	7.9	5.9

TABLE XIII.

Age Group	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.	All ages.
No. of cases	51	28	8	45	10	142
Average No. of days positive.	9.6	8.2	6.8	5.9	6.8	7.8

The number of cases still positive after one course of treatment was 13, that is 9.4%.

They belonged to the following age-groups.

TABLE XIV.

Age Group.	0-2 yrs.	2-5 yrs.	5-12 yrs.	12-60 yrs.	Over 60 yrs.
No. of cases.	10	1	1	1	0
Percentage of total No. in group.	19.6	3.6	12.5	2.2	0

Discussion./

Discussion.

If the series of Sonne cases treated with sulphaguanidine is compared with the two series of Flexner cases similarly treated, it will be seen that, while the average number of days during which the cases remained positive was about the same, the percentage of cases remaining positive after one course of treatment is higher, namely 21.1% compared with 17.6% in the first Flexner series and 13.9% in the second. The series of Sonne cases treated with sulphaguanidine first, and then with succinyl sulphathiazole may also be compared, when it is seen that the percentage of cases still positive after the course of sulphaguanidine was as high as 30.4.

On the other hand the Sonne cases which were treated entirely with succinyl sulphathiazole showed an average number of days positive of 7.8 and the percentage of cases positive after one course of the drug was only 9.4. All of those cases became negative after a second course of succinyl sulphathiazole but one of the cases was positive for 34 days altogether.

In this series of cases it will be noted, therefore, that the results of treating Sonne infections with succinyl sulphathiazole, certainly so far as bacteriological clearance is concerned, were very much better than the results when sulphaguanidine was/

was used. This finding supports the view held in the United States, Hardy and Watt (1944), Painton and Hantman (1945), that succinyl sulphathiazole is the best drug for the treatment of Sonne infections but, on the other hand, Swyer (1945) found that the relapse rate was higher with succinyl sulphathiazole than with sulphanilyl benzamide and sulphanilylamidobenzamide. However he used a much smaller dose, 44 gms. in 5 days, and, with a drug whose action depends on a high concentration in the large intestine, an adequate dosage for a sufficient length of time is essential.

Effect of age on the development of the carrier state.

A point of importance which emerges from a study of the series of cases described above is the fact that, in 5 out of the 7 series of cases, the 0-2 age-group was the one in which the biggest percentage of cases remained positive after a course of treatment; while, again in 5 out of the 7 series, the 12-60 age-group was the one in which the smallest percentage of cases remained positive after treatment. This applies to the first series treated with sodium sulphate as well as to the series treated with sulphonamide, so it has nothing to do with the response to sulphonamide at the different age-groups. It means that, before assessing the results of treatment in bacillary dysentery/

dysentery with any drug, the age-group to which the patients belonged must be known, as, judging by the experience of the 1000 cases just described, the bacteriological results will be much better in adults than in children, especially children under 2 yrs.

Blood levels of sulphaguanidine and succinyl sulphathiazole.

(1) Sulphaguanidine.

In 60 of the cases in the first series treated with sulphaguanidine estimations of the level of "free" sulphaguanidine in the blood were made. Altogether 110 such estimations were carried out, some of the patients having blood removed for examination on two or three occasions. The first specimen was not taken until 24-36 hrs. of treatment had been carried out, and no specimens were taken later than the last day of treatment. Owing to the difficulties of getting blood from young children only adults or older children were used for this purpose.

The "free" sulphaguanidine in the blood was estimated by me at the City Hospital using the method of Bratton and Marshall and a Lovibond Comparator.

Results.

The average blood level of "free" sulphaguanidine in/

in the 110 estimations was 1.9 mgms. per 100 c.c.

The highest level was 6 mgms. per 100 c.c., 1 case had a level of 4.5 mgms, 3 a level of 4 mgms, 1 a level of 3.5 mgms. and 4 a level of 3 mgms.

The remaining 100 specimens had a blood level of under 3 mgms, the lowest amount being a "trace" got on 5 occasions.

The blood level in any one patient tended to remain about the same throughout the course of treatment.

An interesting finding was that, although only 26 out of the 60 patients examined were over 60 yrs. of age, all of the ten patients who had blood levels of 3 mgms. or higher were over 60 yrs. of age, 7 of them being over 70 yrs. of age.

Similar results were got in a further 96 estimations carried out on patients receiving the same course of sulphaguanidine and suffering from "clinical dysentery," but not included in the series under discussion as the infecting organism was never isolated. One of these patients, a man of 74 yrs. had a blood sulphaguanidine level of 7.5 mgms. and another six patients, all over 60 yrs. of age, had blood levels over 3 mgms. per 100 c.c. Less than half of the patients belonged to the over 60 age-group. The average blood-level in this group of cases was 1.7 mgms. per 100 c.c.

<u>Discussion</u>./

Discussion.

The findings described above may be compared with those of Hay (1943) who found that blood-levels of sulphaguanidine varied from 3 mgms. per 100 c.c. to a "trace". He found a concentration of 9 mgms. on one occasion, 8 mgms. on two occasions, 7 mgms. on one occasion and 6 mgms. on one occasion. He was using a slightly smaller dosage of the drug and does not give the ages of the patients examined.

Jamieson and others (1944) remark that, in spite of claims that sulphaguanidine is poorly absorbed from the bowel, surprisingly high concentrations are found in the urine, and, of course, that is evidence of absorption into the blood.

As already noted, Smith (1944) got blood levels of 10-14 mgms. per 100 c.c. after 24 gms. of the drug daily for 2 days and he found that the blood-levels fell as the daily dosage was reduced.

It is therefore evident that, while sulphaguanidine does not reach as high blood-levels for the dosage given as the more readily absorbed drugs, it may, on occasion, reach quite high levels even with the ordinarily used dosage. It may therefore exercise part of its effect through the blood stream, and also toxic effects arising from its presence in the blood and from its excretion by the kidneys might be expected in a proportion of cases.

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No/

No reference in the literature has been found to the fact that relatively high blood-levels of the drug are more likely to occur in old people, but the findings recorded above indicate that special care may be necessary in such cases to ensure an adequate fluid intake. The high levels may be due to a greater absorption from the bowel in old people, or they may be due to a slower excretion of the drug or to a slower acetylation in such cases. The total amount of sulphaguanidine in the blood was not estimated so the amount of acetylated drug present in those cases is not known.

(2) Succinyl sulphathiazole.

22 samples of blood from 11 of the patients treated with succinyl sulphathiazole were examined but only a trace of the drug was found, indeed, on two occasions, none at all could be demonstrated. This is in agreement with the findings of others who have found that only traces of this sulphonamide are absorbed.

Toxin/

Toxic effects of sulphaguanidine and succinyl sulphathiazole.

(1) Sulphaguanidine.

The only toxic effects observed in the whole of the cases treated with this drug were a drug rash, seen on two occasions, and a drug fever seen once. The rashes appeared at the end of one course of the drug and were morbilliform in type, being present on the arms and legs with a few indefinite spots on the trunk. The patients developing them were aged 6 yrs. and 54 yrs. The patient who developed the drug fever was aged 35 yrs., and had a temperature of 101-102°F for two days after the course of sulphaguanidine. No other cause for the pyrexia could be found. Blood sulphaguanidine levels were not estimated in these cases but Smith (1944), who got a high percentage of rashes in his cases treated with big doses of the drug, found no relation between the blood sulphaguanidine - level and the development of a rash. None of the patients in this group who developed a rash or drug fever had been previously treated with any sulphonamide.

(2) Succinyl sulphathiazole.

A few of the adult patients treated with this drug complained of some abdominal discomfort, and there was not such a tendency to constipation as with sulphaguanidine.

Apart/

Apart from this no toxic effects of any kind were observed.

Comment.

In the group of cases under consideration both sulphaguanidine and succinyl sulphathiazole, even in repeated courses, proved to be remarkably free from the risk of toxic side-effects.

Summary.

1. Sulphaguanidine gave clinical results slightly superior to sodium sulphate when used in the treatment of 285 cases and carriers of Flexner dysentery. The average number of days during which diarrhoea was present in the sulphaguanidine-treated cases was 1.7, while in the sodium sulphate-treated cases it was 3.4.

2. After a course of treatment fewer cases in the sulphaguanidine series were bacteriologically positive. The percentages in this first series of cases were 17.6 for the sulphaguanidine-treated cases and 53.3 for the sodium sulphate-treated cases. The average number of days during which those treated with sulphaguanidine remained positive was 8.1 and, for those treated with sodium sulphate, it/

it was 14.7. In a further group of 194 Flexner infections treated with sulphaguanidine in repeated courses if necessary the percentage of cases still positive after the first course was 13.9, and the average number of days during which the cases remained positive was 8.7.

3. In a small group of 87 Newcastle infections similarly treated the percentage of cases still positive after one course of sulphaguanidine was 9.2, and the average number of days during which the cases remained positive was 6.8.

4. In the treatment of Sonne infections succinyl sulphathiazole gave results superior to sulphaguanidine so far as bacteriological clearance was concerned. In 142 cases and carriers of Sonne infection treated with succinyl sulphathiazole, in repeated courses if necessary, only 9.4% was positive at the end of one course of treatment, while in 180 Sonne infections treated with sulphaguanidine 21.1% was positive after one course and, out of another 184 Sonne infections, 30.4% was still positive after one course of sulphaguanidine. The average number of days during which the cases in the first series remained positive was 7.5, in the second series it was 8.8 and in the third it was 9.4. The third series had a first course of sulphaguanidine followed, if necessary, by courses of/

of succinyl sulphathiazole. No control series was treated with sodium sulphate in the case of Sonne infections.

5. In 5 out of 7 of the series of cases studied it was noted that the age-group 0-2 yrs. gave the biggest percentage of cases still positive after a course of treatment. The age-group giving the lowest percentage of positive cases after a course of treatment was, in 5 out of the 7 series, the 12-60 one. This difference in the bacteriological results of treatment in the different age-groups was present in the cases treated with sodium sulphate as well as in those treated with sulphonamides.

6. The average blood level of "free" sulphaguanidine got with the dosage used was 1.9 mgms. per 100 c.c. In 10 out of 110 blood samples examined the amount was 3 mgms or more, the highest amount being 6 mgms. per 100 c.c. These high readings were all got in patients over 60 yrs. of age.

Only a trace of succinyl sulphathiazole was detected in 22 specimens of blood examined.

Sulphaguanidine and especially succinyl sulphathiazole were both very free from toxic side-effects even when given in repeated courses amounting in a few cases to a total amount of 340 gms.

Conclusions.

The results described above are therefore a further demonstration of the value of, and also of the limitations of, sulphaguanidine and succinyl sulphathiazole in the treatment of bacillary dysentery. While showing that sulphaguanidine gives results superior to sodium sulphate in the treatment of Flexner dysentery, they show that, certainly in this instance, it was not nearly as effective in bringing about bacteriological cure in Sonne infections. Succinyl sulphathiazole was much more effective in this respect.

Also, whatever may be the short-comings of the standard of clearance adopted, one thing of importance was demonstrated: at least 10% of Sonne infections treated with succinyl sulphathiazole, and at least about 18% of Flexner infections treated with sulphaguanidine still gave positive cultures after a course of treatment.

The importance of two factors which must be taken into account when the results of the use of sulphonamide drugs in the treatment of this disease are being considered, was brought out namely, the type of the infecting organism and the age of the patient.

It was again demonstrated, as had been shown by previous workers, that repeated courses of the drugs were sometimes necessary to effect bacteriological cure, and that, even in repeated courses, sulphaguanidine and especially succinyl sulphathiazole are very free from the risk of toxic effects.

PART III.

DISCUSSION AND RECOMMENDATIONS FOR TREATMENT.

From a consideration of the published work described above, and from personal experience of treating the 1000 cases just recorded, it can be concluded that all cases of bacillary dysentery - by which is meant all cases of infection with dysentery bacilli, whether they have blood and mucus in the stools or not - should be treated, as soon as possible, and as thoroughly as possible, with a sulphonamide drug, partly because of its effect on the clinical course of the disease, but mainly because of its effect in reducing the number of cases bacteriologically positive after treatment. In this country the latter effect is of much more importance than the clinical effect in the majority of cases.

Choice of sulphonamide.

It has to be decided which of the available sulphonamides should be used. There are available for use in intestinal infections two main groups of the drugs: those, such as sulphanilamide, sulphapyridine, sulphathiazole, sulphadiazine and sulphamerazine which are almost completely absorbed before the large intestine is reached; and those which are either incompletely/

incompletely absorbed such as sulphaguanidine, or hardly absorbed at all such as succinyl sulphathiazole and phthalyl sulphathiazole. There are also the more recently introduced sulphanilylbenzamide and sulphanilylamidobenzamide which are incompletely absorbed. A majority of workers has concluded that there is no qualitative difference between the different sulphonamides - with the exception of marphanil - but that the different clinical effects of the drugs are due to such factors as differing solubility, rate of absorption and excretion, degree of ionisation etc. (M.R.C. war memorandum No.10. 1945). The problem is therefore to decide by which method an adequate concentration of active sulphonamide can be got in contact with the organisms. The great advantage of the poorly absorbed drugs is that they give rise to fewer toxic effects than the others. On the other hand they have to be given in larger doses than the more readily absorbed drugs, and sulphaguanidine at least is a relatively poor bacteriostatic agent. In order to decide whether a drug giving a high blood level of sulphonamide is required, or one which is poorly absorbed and therefore reaches a high concentration in the bowel, some aspects of the pathology of the disease must be considered.

Pathology./

Pathology.

Although bacillary dysentery, in all but the most severe cases, is a local disease of the large intestine and occasionally of the terminal part of the small intestine, the general disturbance being due mainly to toxaemia, Manson-Bahr (1942) states that dysentery bacilli can be seen in sections of the intestine in the muscularis mucosae and especially in the solitary follicles. Bacilli have been recovered in severe cases from the joint effusions in cases of arthritis. Even if it is conceded that, in the ordinary case, the bacilli do not penetrate deeply into the mucous membrane and enter the blood stream in great numbers, it seems reasonable to suppose that they do penetrate a little, and, the more acute the disease, the greater will be the number of organisms which have entered the tissues. Also, in chronic cases, granulations and chronic ulcers develop and the mucous membrane may undergo cystic degeneration, the organisms persisting in the mucous secretion of retention cysts in the bowel wall (Manson-Bahr, 1942).

In view of the pathology described above one would expect that the best results in the acute stage of the disease, and especially in severe cases where organisms are penetrating the tissues, should be got with sulphonamides reaching a high concentration in the blood. That would also seem to be a reasonable method

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of getting the drug into contact with organisms at the bases of ulcers, provided too much fibrous tissue has not formed to wall them off. On the other hand, once the acute infection has subsided and the organisms may be, as suggested by Fairbrother (1944) in the case of Sonne infections, leading a more saprophytic existence in the bowel lumen, then an active sulphonamide in high concentration in the large intestine, that is one which is poorly absorbed, should give the best results, certainly so far as bacteriological clearance is concerned. It would also be expected that, in some cases, where the bacilli are buried in fibrous tissue or in granulations or are deep down in thick-walled cysts, neither sulphonamide in the blood stream or sulphonamide in the lumen of the intestine would reach the organisms.

Sulphonamide-sensitivity of the organism.

The other theoretical consideration when deciding which sulphonamide will be most effective, is the sensitivity to sulphonamide of the different types of dysentery bacilli.

Marshall and others (1940) claimed that sulphaguanidine was inhibitory, bacteriostatic and bactericidal in vitro for organisms of the dysentery group. Brewer (1944) found that Sonne strains were inhibited by succinyl sulphathiazole but that sulphaguanidine was relatively ineffective. This result was confirmed by Fairbrother/

Fairbrother (1944) who found that Flexner organisms gave the same results. Jamieson and others (1944) found that sulphaguanidine was bacteriostatic but not markedly so for a Flexner strain, Sonne III and Shiga organisms. Brodie and others (1946) demonstrated that phthalyl sulphathiazole had a bacteriostatic effect on Flexner, Sonne III and Newcastle organisms which was more pronounced when a semi-solid medium was used; and Poth and Ross (1944) had shown that phthalyl sulphathiazole had twice the bacteriostatic effect of succinyl sulphathiazole on coliform organisms. It therefore appears that, in vitro, sulphaguanidine is not as active against dysentery bacilli as succinyl sulphathiazole and that this is most marked when the Sonne bacillus is used, as the Flexner organism responds to the less active drug. Phthalyl sulphathiazole appears to be still more active.

From those laboratory findings one would expect succinyl sulphathiazole and phthalyl sulphathiazole to be more effective than sulphaguanidine under those circumstances discussed above where a poorly absorbed sulphonamide is required.

Clinical findings.

In fact, a good deal of support for the conclusions arrived at from a consideration of the pathology and bacteriology of the disease is got from the published results/

results of the clinical use of the drugs. It has been found that the readily absorbed sulphonamides have usually given results as good as, and in some cases better than, the less readily absorbed drugs, in the clinical cure of the disease, and especially in the treatment of severe cases. This has been found in this country, in the United States and by those treating cases in the forces. The best bacteriological results, on the other hand, following treatment of the more resistant Sonne type of organism have been got with poorly absorbed drugs such as succinyl sulphathiazole. Also, even with the use of this drug in big doses, there is still a percentage of failures.

Dosage of sulphonamides.

So far as dosage of the drugs in this disease is concerned, a relatively small dose of the readily absorbed sulphonamides has proved adequate; in the case of sulphadiazine, Scadding (1945) found 3 gm. daily sufficient in mild cases. As sulphadiazine is very slowly excreted an adequate blood-level of the drug can be maintained with three or four doses given during the day. The small dosage has some advantage where large numbers are being treated and where infants and young children are concerned. In very severe cases an initial dose of the readily absorbed drugs can be given intravenously.

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The poorly absorbed drugs at present in use require to be given in bigger doses so as to saturate the contents of the gut. The good results in Sonne infections got at the City Hospital with succinyl sulphathiazole were got with a dosage of 12 gms. a day for 7 days. As this drug is hardly absorbed at all no general toxic effects are likely to arise with big doses and the big doses are more likely to result in the drug reaching all parts of the folded mucous membrane of the bowel. Where sulphaguanidine is concerned, although toxic effects are few and unimportant, they do occur, as demonstrated by Smith (1944) and Brewer (1943) if big doses are given; and indeed, in sensitive cases, with small doses (Smith 1944). At least 12 gms. a day, which was the dosage employed at the City Hospital where negligible toxic effects were got, is probably required and some workers, for example Brewer (1943) recommend bigger doses in chronic cases. There would seem to be no need for giving the drug more than four times daily, and it seems reasonable to give a larger dose in the first 24 hrs. to attempt to saturate the bowel contents as soon as possible. The big doses of the poorly absorbed drugs which are required are a disadvantage where big numbers have to be treated and also where children are concerned.

The duration of treatment required will depend on the severity of the disease but probably a minimum of/

of 5 days treatment is necessary even in mild cases, and 8 to 10 days treatment at a time is required to get the best results in chronic cases and carriers. It has been shown at the City Hospital, and also by others, that repeated courses of the less readily absorbed drugs can be given without toxic effects.

Recommendations for treatment.

It is therefore recommended that acute cases of bacillary dysentery be treated with one of the readily absorbed sulphonamides in doses of 4 to 6 or more grammes daily depending on the severity of the disease. This should be continued until the acute stage is passed as judged by the disappearance of pyrexia and of blood and mucus from the stools, and by the stools becoming less frequent and formed. As sulphanilamide and sulphapyridine are more liable to give undesirable toxic effects and, as good results have been got with sulphathiazole and sulphadiazine, the latter would seem to be the drugs of choice. Although no published work has been found on the results of the use of sulphamerazine, on theoretical grounds it should prove satisfactory. It is submitted that, in cases endangering life, the toxic effects from the use of those drugs are no bar whatever to their use, if it has been shown that they act more quickly in such cases and have a more marked effect on the course of the disease.

Likewise,/

Likewise, in all really acute cases, the benefits of the drugs seem to outweigh any disadvantages. It is suggested that, after the acute stage of the disease is passed - and this applies especially to Sonne infections - full doses of the most active poorly absorbed sulphonamide be given for a period of at least 5 days. At present succinyl sulphathiazole appears to be the most active of those drugs, but phthalyl sulphathiazole may prove more active in big doses.

Sulphaguanidine, although it is not as active in dealing with organisms in the bowel as succinyl sulphathiazole, and, although it does not act as quickly on the acute symptoms as the readily absorbed drugs, does seem to combine the two effects to a certain extent; and it gives fewer toxic effects than the readily absorbed drugs. It does, therefore, seem to have a sphere of usefulness in treating mild infections with Flexner or Newcastle types of organism, where toxic effects are undesirable. Nevertheless it is just in that type of case that resistant infections are likely to arise and more active drugs may have to be resorted to. Of course, in all severe cases, abundant fluids must be given, parenterally if necessary, especially if sulphonamide drugs which may cause blockage of renal tubules are being used. The diet need not be unduly restricted in mild cases, but should be light as long as diarrhoea is present.

Although/

Although it is hoped that, by the above active measures in acute cases, the number of cases bacteriologically positive after treatment will be reduced, it is obvious, from recorded clinical experience, that a percentage of cases will remain positive after the course of treatment outlined above. There also remain for consideration the contact carrier and the case which comes under observation only when the convalescent carrier state is established. It is suggested that, in all of those cases, a few days treatment should be given with a readily absorbed sulphonamide which will reach any organisms accessible from the blood stream; after that full doses of succinyl sulphathiazole, or of any more active poorly absorbed drug which may become available, should be given for a period depending on the length of time for which the carrier state has been known to exist. A course of 14 days or repeated courses may be necessary if the carrier state is of long standing. It is also suggested that, before treatment with a poorly absorbed sulphonamide is begun, the bowel should be emptied, as far as possible, by two or three doses of sodium sulphate in the 24 hrs. preceding treatment; and that diet during the course should be very light so as to reduce the amount of residue in the large intestine, and so allow a greater chance of the drug reaching the whole surface of the mucous membrane. It has to be remembered, in cases receiving/

receiving long courses of poorly absorbed sulphonamides that, owing to destruction of bacilli which are normal inhabitants of the bowel, vitamin synthesis may be interfered with. An adequate supply, especially of the vitamin B. group should therefore be ensured.

In cases which remain positive in spite of a course such as this it may be worth while having the organism tested for sulphonamide sensitivity, as it may be a sulphonamide resistant strain or it may have acquired resistance to sulphonamides.

The treatment of the more severe type of case due to infection with the Shiga bacillus, which is rarely seen in this country, is not really being considered in this discussion, but combined with serum treatment, sulphonamides have apparently proved effective in such cases. Those who have experience of the treatment of the chronic type of case advise sigmoidoscopy to find out the condition of the bowel mucous membrane, and prolonged treatment with sulphonamides until healing has taken place. It would therefore seem advisable, in really persistent carriers in this country, to carry out sigmoidoscopic examination to find whether there is any lesion of the mucous membrane which is the cause of the carrier state.

In conclusion it may be stated that, while the use of drugs of the sulphonamide group in the treatment of bacillary dysentery is a definite advance in the therapy/

therapy of that disease, it is still not possible to effect bacteriological cure of the disease in every case. The best results obtainable at present can only be got by a study of the individual requirements of each case and by the use of both the readily absorbed sulphonamides and those which are poorly absorbed and therefore reach a high concentration in the large bowel. Further advances in therapy await the introduction of a drug more active against dysentery bacilli, and also a better understanding of the reasons for the development of dysentery carriers.

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